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TOTAL AMOUNT OF PAYMENT	$340

Complete if Known	
Application Number	10/030,378
Filing Date	November 9, 2001
First Named Inventor	Blue, Jeffrey T.
Examiner Name	Le, Emily M.
Group Art Unit	1648
Attorney Docket Number	20455P

METHOD OF PAYMENT

☒ Deposit Account

Deposit Account Number: 13-2755 Deposit Account Name: Merck & Co., Inc.

The Director is authorized to:

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FEE CALCULATION

FEES
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Fee Code	Fee ($)	Fee Description	Fee Paid
1051	130	Surcharge - late filing fee or oath	
1051	130	Non-English Specification	
1812	2,520	For filing a request for *ex parte* reexamination	
1402	340	Filing a brief in support of an appeal	340
1452	110	Petition to revive - unavoidable	
1453	1,370	Petition to revive - unintentional	
1460	130	Petitions to the Commissioner	
1807	50	Processing fee under 37 CFR 1.17(q)	
1806	180	Submission of Information Disclosure Statement	
1809	790	Filing a submission after final rejection (37 CFR 1.129(a))	
1810	790	For each additional invention to be examined (37 CFR 1.129(b))	
		Other fee (specify) _____	
		Other fee (specify) _____	
		TOTAL	$340

SUBMITTED BY				Complete (if applicable)	
Typed or Printed Name	Sheldon O. Heber			Reg. Number	38,179
Signature		Date	05/04/2005	Deposit Account User ID	

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MERCK & CO., INC.

By _____ **Date** 5-4-05

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Appellant: Blue, Jeffrey T.

Application Number: 10/030,378

Attorney Docket Number: 20455P

Filing Date: November 9, 2001

Title of the Invention: Detection of Viral Stability

Examiner: Le, Emily M

Art Unit: 1648

APPEAL BRIEF

37 C.F.R. 1.8 Certificate of Mailing

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MERCK & CO., INC.

By _____ Date May 4, 2005

Sheldon Heber

TABLE OF CONTENTS

REAL PARTY IN INTEREST

The real party in interest is Merck & Co., Inc. Jeffery T. Blue is the listed inventor.

RELATED APPEALS AND INTERFERENCES

There are no related appeals and interferences.

STATUS OF CLAIMS

Claims 1-8, 18 and 19 are pending; and claims 9-17 are canceled. The rejection of claims 1-8, 18 and 19 is being appealed.

STATUS OF AMENDMENTS

In response to an initial final rejection mailed July 7, 2004, applicants canceled withdrawn claims 9-17. The office action mailed November 11, 2004 entered the amendment canceling claims 9-17, vacated the prior final rejection and provided a new final rejection. No amendments to the claims were filed with respect to the final rejection dated November 11, 2004.

SUMMARY OF CLAIMED SUBJECT MATTER

The pending claims are directed to a method measuring viral induced caspase 3 activity as an indication of virus activity. Independent claim 1 comprises the steps of: (a) contacting a plurality of cells susceptible to caspase 3 induction with a virus, were the virus induces caspase 3 activity; and (b) "measuring said caspase 3 activity as an indication of virus activity".

Measuring viral induced caspase 3 activity provides an alternative assay to using a plaque forming unit (PFU) assay to measure viral activity. The PFU assay measures viral activity based on the ability of a virus to infect cells and cause plaque formation, or areas on dead or detached cell. (The application at page 1, lines 11-20.)

The application includes examples illustrating a correlation between viral induced caspase 3 activity and virus activity, and the reproducibility and linearity of the caspase 3 assay. The application also illustrates using the caspase 3 assay to measure viral activity, viral potency, and viral stability in samples under different conditions.

A correlation between viral activity and caspase 3 signal is illustrated in the application using different viral dilutions and by comparing results obtained with the caspase 3 assay to results obtain with a PFU assay. The effect of different viral dilutions is summarized in Tables 5 and 6. (The application on page 11, line 5 to page 12, line 2.) As the multiplicity of infection decreased through viral dilution, caspase 3 signal correspondingly decreased. Figures 4-6 provide results comparing the caspase 3 assay to a PFU assay.

The reproducibility of the caspase 3 assay is illustrated in the application by repeating the assay using three vials of the same sample. (The application at page 10, line 19 to page 11, line 4, including Table 4). Table 4 illustrates that, overall, the assay is reproducible.

The linearity of the caspase 3 assay is illustrated by measuring caspase 3 activity at different time following viral induction. (The application at page 9, lines 1-11 and Figures 2a and 2b.) Figure 2a illustrates that the assay is linear for at least one hour using measles virus. Figure 2b illustrates that the assay is linear for at least 75 minutes using mumps virus.

Figure 3 provides viral activity for different samples in RFU (reflective fluorescent units). (The application at page 2, lines 22-26 and page 12, lines 4-13.) The RFU for a particular sample provided a direct measure of viral potency. The RFU from different samples provided a measure of viral stability under the different conditions.

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

I. Claims 1-8, 18 and 19 stand rejected under 35 U.S.C. §112, first paragraph, for allegedly failing to comply with the enablement requirement

ARGUMENT

I. Claims 1-8, 18 and 19 are Enabled

Claims 1-18, 18 and 19 are directed towards a method measuring viral induction of caspase 3 activity as an indication of virus activity. The application provides sufficient guidance for the skilled artisan to practice the invention without undue experimentation. The guidance provided in the application includes a brief description of the prior art PFU assay along with examples illustrating: (1) a correlation between viral activity and viral induced caspase 3 activity; (2) the reproducibility of the caspase 3 assay; (3) the linearity of the caspase 3 assay; and (4) the use of the viral induced caspase 3 activity to measure viral activity, viral potency and viral stability. (The Application on page 1, lines 11-20 and pages 5-12, discussed in the Summary of the Claimed Subject Matter *supra.*)

Separate arguments are presented for the different groups of rejected claims. The claims are argued separately as follows: (A) claims 1-3 and 6-8; (B) claims 4 and 18, wherein the virus is either measles, mumps, or rubella virus; and (C) claims 5 and 19, wherein the plurality of cells is either Vero cells or RK-13.

A. Claims 1-3 and 6-8

The enablement rejection is based on the examiner interpreting viral activity as viral stability and viral potency. (Advisory Action mailed 04/21/2005, Continuation Sheet, reason (i).) The examiner argues that it is unclear how a correlation between viral induced caspase 3 activity and viral activity can be used to determine viral stability and potency activity. (Advisory Action mailed 04/21/2005, Continuation Sheet, reason (ii).) The examiner also argues that the application does not teach the skilled artisan how to account for apoptosis. (Advisory Action mailed 04/21/2005, Continuation Sheet, reason (iii).)

Enablement requires the specification to teach the skilled artisan to make and use the invention without undue experimentation. *In re Wands,* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Determining what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. *Id.* A considerable amount of experimentation is permissible,

if it is merely routine, or if the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. *Id.*

The pending claims are directed to measuring viral activity. The application provides sufficient guidance for the skilled artisan to measure viral activity using the claimed assay without undue experimentation. While the claims are directed to measuring viral activity, the present application illustrates using viral activity obtained from the caspase 3 activity as a measure of viral potency, and stability by analogy to the PFU assay described in the Background of the Invention and in resulted illustrated in Figure 3.

Viral potency and stability can be determined based on the viral activity obtained from caspase 3 induction in the same manner in which viral activity from the PFU assay is used to determine viral potency and stability. The Background of the Invention briefly describes the use of the PFU assay. The PFU assay measures viral activity by measuring the ability of a virus to form plaques. Different viral dilutions are tested in the PFU assay. The number of plaques in a PFU assay provides the viral activity from a particular solution. Viral potency based on the number of plaques is readily determined by taking into account the viral dilutions performed in the assay. Viral stability is determined with a PFU assay by examining a change in PFU over time. (The application at page 1, lines 9-20.)

The present application in Figure 3 provides viral activity measurements for different samples based on the caspase 3 assay in RFU. (The application at page 2, lines 22-26 and page 12, lines 4-13.) The RFU for a particular sample provides a direct measure of viral potency. The RFU from different samples provides a measure of viral stability under the different conditions.

1. <u>The Present Application Does Not Equate Viral Activity with Viral Stability and Potency</u>

The present application does not equate viral activity with viral potency and stability. The application clearly indicates that viral activity can be used to provide a **measure** of viral potency and stability in both the first paragraph under the heading of Summary of the Invention, and the Abstract:

> Viral induction of caspase 3 activity was found to provide a reliable **measure** of viral activity. Assaying viral induction of caspase 3 activity can be used, for example, in methods for **measuring viral potency and stability**, and for evaluating the stability of a virus in different formulations. [Emphasis added.]

(The application at page 1, lines 23-26, and the Abstract.)

Consistent with the first paragraph of the Summary of the Invention and the Abstract, claim 1 is directed to assaying viral activity by measuring viral induced caspase 3 activity. The caspase 3 assay described in the present application provides an alternative to measuring viral activity using the PFU assay.

2. Use of Viral Activity to Obtain Viral Stability and Potency

The Examiner acknowledges the application supports a correlation between viral activity and viral caspase 3 induction, but argues that it is unclear how the correlation can be used to measure viral potency and activity. (Advisory action mailed 04/21/2005, Continuation Sheet, reason (ii).)

Viral activity, potency and stability are related concepts. Viral activity measurements can readily be used by the skilled artisan to determine viral potency and stability. Determination of viral potency and stability based on viral activity can involve additional steps illustrated in the application and well known in the art. For example, viral activity may directly correspond to the potency of an original solution or, if dilutions of the solution are made, viral potency for the original solution would take into account viral dilutions. Determination of viral stability based on viral activity can involve additional steps such measuring activity over time, under different conditions or different formulations. (See the application at page 1, lines 11-20 and page 2, lines 2-4.)

3. Apoptosis

The examiner argues that the application does not provide guidance on how to account for caspase 3 playing a key role in initiation of cellular events during early apoptotic process. (Advisory action mailed 04/21/2005, Continuation Sheet, reason (iii).) Villa et al., (TIBS, Vol. 22, pps. 388-393, 1997) was previously cited for teaching cells undergo apoptosis in response to

a wide range of environmental cues. (Office Action mailed 03/15/2004 at page 7, middle of the first paragraph.)

The examiner fails to provide evidence that apoptosis is a concern under those conditions used the assay. Villa et al., simply refers to some undefined environment hues. The Patent Office bears the initial burden of presenting a *prima facie* case of unpatentability. *In re Oetiker* 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992).

Additionally, the examples provided in the application illustrate that conditions exist under which apoptosis does not prevent the assay from being used. The skilled artisan selects the conditions under which the assay is performed. The virus itself can be taken from different environments and assayed in cells under suitable conditions where apoptosis would not prevent the assay from being used.

B. Claims 4 and 18

Claims 4 and 18 further describe the invention by indicating the virus is either measles, mumps or rubella virus. Measles, mumps, and rubella virus were used in examples to illustrate the assay. (The application on page 5-12.) Such examples illustrate that the claimed assay can generally be used for different types of viruses and specifically illustrate the use measles, mumps or rubella virus.

C. Claims 5 and 19

Claims 5 and 19 further describe the invention by indicating the cell used in the assay is either Vero cells or RK-13. The examples provided in the application illustrating viral induction of caspase 3 activity generally employed Vero plates for measles and mumps virus infections, and RK-13 cells for rubella virus infection. (The application at page 6, lines 15-16.) Such examples illustrate that the claimed assay can generally be used with different cell types and specifically illustrate the use of Vero cells and RK-13.

CONCLUSION

Appellant request that the Board of Patent Appeals and Interferences reverse the outstanding rejections of claims 1-8, 18 and 19.

Please charge deposit account 13-2755 for fees due in connection with this appeal brief. If any time extensions are needed for the timely filing of the present appeal brief, appellant petition for such extensions and authorize the charging of deposit account 13-2755 for the appropriate fees.

Respectfully submitted,

By 

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CLAIMS APPENDIX

1. A method for assaying activity of a virus comprising the steps of:

(a) contacting a plurality of cells susceptible to caspase 3 induction with said virus, wherein said virus induces caspase 3 activity; and

(b) measuring said caspase 3 activity as an indication of virus activity.

2. The method of claim 1, wherein said caspase 3 activity is measured using a caspase 3 substrate linked to a fluorimetric or a colorimetric moiety.

3. The method of claim 2, wherein said substrate is the peptide Asp-Glu-Val-Asp (SEQ ID NO: 1).

4. The method of claim 3, wherein said virus is either measles virus, mumps virus, or rubella virus.

5. The method of claim 4, wherein said plurality of cells is either Vero cells or RK-13 cells.

6. The method of claim 3, wherein prior to said step (a) said virus was lyophilized.

7. The method of claim 3, wherein viral activity is assayed at two or more different time intervals by performing said step (a) followed by said step (b) at two or more time intervals.

8. The method of claim 3, wherein after said step (a) and prior to said step (b) said cells were frozen and then thawed.

18. A method for assaying activity of a virus comprising the steps of:

(a) contacting a plurality of cells susceptible to caspase 3 induction with said virus, wherein said virus is either measles virus, mumps virus, or rubella virus; and

(b) measuring said caspase 3 activity as an indication of virus activity.

19. The method of claim 18, wherein said plurality of cells is either Vero cells or RK-13 cells.

EVIDENCE APPENDIX

None

RELATED PROCEEDINGS

None